REMARKS

Status of the Claims

By this amendment, claims 10 and 30 are canceled and claims 1, 12, 18 and 32 are amended. Upon entry of this Amendment, claims 1-9, 11-21, 23-29 and 31-37 will be pending in the application. The cancellation of claims does not constitute acquiescence in the propriety of any rejection set forth by the Examiner.

Claim Rejections - 35 U.S.C. § 102

Claims 1-4, 6, 8, 13-14, 18-19, 23-24, 26, 28 and 33-34 are rejected by the Examiner under 35 U.S.C. § 102 as being anticipated by Hammond et al. as evidenced by U.S. Patent No. 5,225,180. The Examiner asserts that the present claims are anticipated by Hammond et al. because Hammond et al. teach a method of administering to a patient a radiolabeled imaging protein conjugate with a D-lysine to reduce the renal uptake in the kidney. The Examiner notes that the protein conjugate of Hammond et al. is a somatostatin analog, is not an antibody or antibody conjugate and is less than 60 kD. Applicants respectfully request reconsideration and withdrawal of the rejection.

The present method, as amended, involves administering to a patient one or more compounds selected from the group consisting of D-lysine, poly-lysine having a molecular weight in the range 1-60 kD, pharmaceutically acceptable salts thereof and carboxyl derivatives thereof. The Examiner asserts that the method of Hammond et al. involves administering D-lysine to a patient. Applicants respectfully disagree with the Examiner. In the right panel of page 1437 of Hammond et al. it states that the Synthamin 14 that was used contained lysine and arginine. It is well known to those of skill in the art, that when an amino acid is recited without a D or L preceding it, one can assume that the amino acid is in the L configuration. Those of skill in the art know that the L isomer is the natural form of an amino acid. Since Hammond et al. used Syntamin 14, and Synthamin 14 does not contain D-lysine, the method of Hammond et al. does not anticipate the present claims.

Claim Rejections - 35 U.S.C. § 103

Claims 1-21 and 23-37 are rejected by the Examiner under 35 U.S.C. § 103 as being unpatentable over Behr et al. (Cancer Research 55:3825-3834, 1995), and further in view of Grey et al. (U.S. Patent No. 5,380,513) and Raines et al. (U.S. Patent No. 5,840,296). Applicants respectfully request reconsideration and withdrawal of the rejection.

The Examiner asserts that Behr et al. teach a method of reduction of renal uptake of a protein conjugate comprising an imaging or therapeutic moiety in a patient with addition of lysine and poly-lysine. However, the Examiner notes that Behr et al. fails to teach a protein conjugate that is not an antibody conjugate or a conjugate comprising a ribonuclease. The Examiner asserts that Grey et al. and Raines et al. cure the deficiencies of Behr et al. because Grey et al. teach a method to reduce renal retention of protein conjugates with lysine and Raines et al. teach conjugates comprising rirbonuclease which have been effective in tumor patients and that the decrease in renal function of Onconase may be the consequence of an inability to effectively clear the Onconase protein from the kidneys.

The Examiner has failed to establish a *prima facie* case of obviousness because all three of the criteria required to establish a *prima facie* case of obviousness have not been met. In order to establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references (or references when combined) must teach or suggest all the claim limitations. See MPEP 2142.

A. The Cited References, As Well As The Knowledge Generally Available To Those Of Skill In The Art, Fail To Provide A Suggestion Or Motivation To Those Of Ordinary Skill In The Art To Combine The Teachings Of The Cited References In Order To Carry Out The Claimed Method

The teachings of Behr et al., Grey et al. and Raines et al. do not provide a suggestion or motivation to those of ordinary skill in the art to combine the teachings in order to carry out the presently claimed method of reducing kidney retention of a protein conjugate. The present method involves administering D-lysine, poly-D-lysine having a molecular weight in the range 1-60 kD, pharmaceutically acceptable salts thereof or carboxyl derivatives thereof. With respect to Behr et al., although Behr et al. teach that D- and L- isomers of lysine were equally effective at reducing kidney uptake of antibody fragments (based on experiments involving radiometals, as well as iodine, bound to Fab' or $F(ab')_2$ fragments), a person of ordinary skill in the art would not assume that D- and L- isomers of lysine would also be equally effective at reducing kidney uptake of a protein conjugate that is not an antibody conjugate. Firstly, a person of ordinary skill in the art would know that the unique structure and properties of antibodies and antibody fragments as compared to protein conjugates that are not antibody conjugates, would likely cause a difference in the effectiveness of D- and L-isomers of lysine at reducing the kidney uptake of antibodies and antibody fragments as compared to protein conjugates that are not antibody conjugates. Secondly, a person of ordinary skill in the art would not automatically expect that D- and L-lysine would behave similarly because a person of ordinary skill in the art would know that D and L amino acids can have dramatically different effects when administered to a patient.

Turning to Grey et al., although Grey et al. teach a method for reducing renal retention of protein conjugates involving administering lysine, Grey et al. fail to teach the use of "D-lysine". As discussed above, a person of ordinary skill in the art would know that when an author recites an amino acid that is not preceded by either D or L, the author is referring to the L isomer of the amino acid. Since Gray et al. recite only "lysine", and not "D-lysine", a person of ordinary skill in the art would know that Gray et al. is directed to L-lysine and not D-lysine. While Gray et al. shows a reduction in renal retention when L-lysine is administered, a person of ordinary skill in the art would not assume that similar results could

be achieved with D-lysine. The L and D isomers of amino acids have very different properties and cause different effects when administered to a patient. A person of ordinary skill in the art would not have been motivated to combine the teachings of Gray et al. with the teachings of Behr et al. in order to arrive at the method of the present invention because Grey et al. do not teach the use of D-lysine. Grey et al. only teach using "lysine".

Finally, Raines et al. fails to disclose using D-lysine in a method for reducing renal retention of protein conjugates that are not antibody conjugates. Therefore, Raines et al. does not cure the deficiencies of Behr et al. and Grey et al.

B. A Person Of Ordinary Skill In The Art Would Not Have Had A Reasonable Expectation Of Success In Combining The Cited Art Teachings In Order To Arrive At The Claimed Method

Not only do the cited references fail to contain a suggestion or motivation to combine the teachings of Behr et al., Grat et al. and Raines et al., but additionally, a person of ordinary skill in the art would not have had a reasonable expectation of success in combining the cited art teachings in order to arrive at the claimed method. As discussed above, a person of ordinary skill in the art would know that the unique structure and properties of antibodies and antibody fragments as compared to protein conjugates that are not antibody conjugates, would likely cause a difference in the effectiveness of D- and L- isomers of lysine at reducing the kidney uptake of antibodies and antibody fragments as compared to protein conjugates that are not antibody conjugates. Therefore, a person of ordinary skill in the art familiar with teachings of Behr et al. would not have expected D-lysine to be effective at reducing the kidney uptake of protein conjugates that are not antibody conjugates. Since Gray et al. discloses L-lysine and not D-lysine, Gray et al. would not have caused a person of ordinary skill in the art to have any greater expectation of success in employing the presently claimed method. Finally, Raines et al. does not cure the deficiencies of Behr et al. and Gray et al. Therefore, a person of ordinary skill in the art would not have had a reasonable expectation of success in combining the teachings of Behr et al., Grat et al. and Raines et al. in order to arrive at the present method.

As discussed above, the Examiner has failed to establish a *prima facie* case of obviousness. The cited references, as well as the knowledge generally available to those of skill in the art, fail to contain a suggestion or motivation to combine the teachings of Behr et al., Gray et al. and Raines et al. in order to arrive at the present method. Additionally, a person of ordinary skill in the art would not have had a reasonable expectation of success at arriving at the claimed method from the combined teachings of Behr et al., Gray et al. and Raines et al. Therefore, the present method is not obvious over Behr et al., Gray et al. and Raines et al.

CONCLUSION

As the above-presented amendments and remarks address and overcome all of the rejections presented by the Examiner, withdrawal of the rejections and allowance of the claims are respectfully requested.

If the Examiner has any questions concerning this application, he or she is requested to contact the undersigned.

Respectfully submitted,

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Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.

Version with Markings to Show Changes Made

1. (4X Amended) A method of reducing kidney retention of a protein conjugate in a patient, comprising administering to said patient one or more compounds selected from the group consisting of D-lysine, poly-[D-]lysine having a molecular weight in the range 1-60 kD, [poly-L-lysine having a molecular weight in the range 1-60 kD,] pharmaceutically acceptable salts thereof and carboxyl derivatives thereof, wherein said protein conjugate has a molecular weight that is not greater than about 60 kD and is not an antibody or antibody fragment conjugate,

wherein the pharmaceutically acceptable [salts] salt and carboxyl [derivatives] derivative of poly-[D-]lysine [or poly-L-lysine have] has a molecular weight in the range 1-60 kD,

whereby said compound or compounds reduce kidney retention of said conjugates.

12. (Amended) The method according to claim 1, wherein said poly-[D-] lysine [and said poly-L-lysine each have] has a molecular weight of 15-30 kD.

18. (4X Amended) A method of reducing kidney retention of a protein conjugate in a patient undergoing treatment with a targeting protein conjugate comprising administering to said patient, one or more compounds selected from the group consisting of D-lysine, poly-[D-]lysine having a molecular weight in the range 1-60 kD, [poly-L-lysine having a molecular weight in the range 1-60 kD,] pharmaceutically acceptable salts thereof and carboxyl derivatives thereof, wherein said protein conjugate has a molecular weight that is not greater than about 60 kD and is not an antibody or antibody fragment conjugate,

wherein the pharmaceutically acceptable [salts] salt and carboxyl [derivatives] derivative of poly-[D-]lysine [or poly-L-lysine have] has a molecular weight in the range 1-60 kD,

whereby said compound or compounds reduce kidney retention of said conjugates.

32. (Amended) The method wherein said poly-[D-]lysine [and said poly-L-lysine each have] has a molecular weight of 15-30 kD.